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Exploring Natural Products to Control Type 2 Diabetes Mellitus through Targeting Advanced Glycation End Products

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Abstract

Objective: Cardiovascular disease (CVD) and diabetes mellitus (DM) are the pressing global health issue, with advanced glycation end products (AGEs) playing a crucial role in its development. AGEs are harmful compounds formed through chronic exposure to elevated blood glucose levels and oxidative stress, both of which are prevalent in diabetes mellitus. These molecules have detrimental effects on vascular function, inflammation, and oxidative stress, exacerbating CVD progression. Conventional strategies for managing AGEs are often limited by side effects and insufficient efficacy, driving the need for alternative approaches. This review investigates the intricate relationship between AGEs, diabetes mellitus, and CVD, with a focus on the therapeutic potential of natural products-particularly phenolic compounds. The review explores how AGEs contribute to the pathogenesis of diabetes-related complications and their impact on cardiovascular health. It examines the molecular mechanisms underlying AGE formation and the inhibitory effects of various natural compounds on this process. Additionally, the review assesses preclinical and clinical evidence supporting the efficacy of these natural agents in mitigating AGE-induced damage. By highlighting the significant role of AGEs in diabetes and CVD, the study underscores the potential of natural products to counteract AGE accumulation. It provides an in-depth analysis of AGE biochemistry, their sources, and the effects of different natural products on AGE formation. The review concludes by emphasizing the promise of natural compounds in reducing oxidative stress and inflammation, and thereby lowering the risk of cardiovascular complications associated with diabetes. This comprehensive overview advocates for the integration of natural products into therapeutic strategies for managing AGE-mediated cardiovascular and diabetic conditions.

Keywords: Advanced glycated end product, Diabetes, Cardiovascular disease, Natural products

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Introduction

Cardiovascular disease (CVD) and diabetes mellitus (DM) remains the leading global health concerns, contributing significantly to morbidity and mortality rates (1). The complex pathophysiology of DM involves various risk factors, among which advanced glycation end products (AGEs) have gained increasing attention in recent years (2). AGEs are a diverse group of molecules formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids, resulting from prolonged exposure to high blood glucose levels and oxidative stress. The accumulation of AGEs is implicated in the progression of CVD through their detrimental effects on vascular function, inflammation, and oxidative stress (3).While therapeutic strategies aimed at reducing AGEs have shown promise; conventional approaches often come with limitations and side effects. In this context, the search for alternative and complementary therapies has led to a growing interest in natural products, particularly those rich in phenolic compounds. Phenolic compounds are well-known for their antioxidant and anti-inflammatory properties, and emerging evidence suggests that they may play a pivotal role in inhibiting AGE formation and mitigating the adverse effects of AGEs on cardiovascular health (4).

This comprehensive review article explores the intricate relationship between AGEs and cardiovascular disease, shedding light on the molecular mechanisms underlying AGE synthesis and their impact on CVD pathogenesis. Furthermore, we delve into the potential therapeutic benefits of natural products and phenolic compounds as novel strategies to counteract AGE accumulation and its detrimental consequences on cardiovascular health. By synthesizing the latest research findings and insights, this review aims to provide a comprehensive evaluation of the therapeutic potential of natural products in the context of AGE-mediated cardiovascular disease.

In the following sections, we will dissect the intricate pathways involved in AGE formation, elucidate the mechanisms through which natural products and phenolic compounds exert their inhibitory effects on AGE synthesis, and critically assess the existing preclinical and clinical evidence. Ultimately, our goal is to pave the way for a deeper understanding of the therapeutic potential of these natural compounds and their integration into future cardiovascular disease management strategies.

All tissues and body fluids endogenously produce AGEs because of glycation processes under physiological conditions. AGEs are less chemically diverse than exogenous sources because they are biologically produced at lower temperatures (5,6). AGEs include fluorescent cross-linking compounds like pentosidine as well as fluorescent or non-fluorescent cross-linking products like methylglyoxal-lysine dimers (MOLD), carboxymethyllysine (CML), and pyrraline (pyrrole aldehyde) (7) . Other than exogenous and endogenous sources of AGEs, some environmental factors like smoking and sedentary lifestyle are thought to contribute to the AGEs synthesis (8,9). In the human body, unregulated glycemic control induces oxidative stress, which is the main contributor to increasing serum AGEs levels. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) promote endogenous glycation events (10). These AGE levels interact with RAGE (advanced glycation end products) and start an extensive signalling pathway which induces inflammatory cytokines and further exacerbates oxidative stress (11,12).

Since diabetes mellitus is the prototype disease marked by excessive formation of AGEs and their build-up, it contributes to morbidity and death from cardiovascular diseases in diabetic people. Diabetes, metabolic syndrome, and cardiovascular disorders are the three main illnesses linked to high AGE blood levels. AGEs have been

associated with a number of diseases, including pancreatic cancer, colorectal cancer, and Alzheimer's disease (13) AGEs may contribute to the onset of cardiovascular disease in those with chronic inflammatory diseases. Atherosclerosis develops more quickly because of AGEs because they suppress vasodilation, interfere with nitric oxide, increase vascular permeability, neoangiogenesis, and stiffness of the arteries (14). In patients with diabetes mellitus, lowering blood AGEs levels is an effective way to alleviate the burden of cardiovascular disease. Certain authors briefly discuss the characteristics of both natural and synthetic drugs that prevent the formation and/or breakdown of existing AGEs (15,16). In the present review, we'll discuss the significance of AGEs in cardiovascular disease, with a focus on how they work to affect intracellular and extracellular signalling pathways, as well as the therapeutic potential of anti-AGEs drugs (both synthetic and natural) to treat cardiovascular disease.

Biochemistry of AGEs

AGEs are a complex group of compounds formed through a series of chemical reactions known as the Maillard reaction or glycation. The Maillard reaction is a non-enzymatic reaction that occurs between reducing sugars and amino groups of proteins, lipids, and nucleic acids. AGEs are implicated in various age-related diseases and diabetic complications (17). The synthesis of AGEs can be broadly divided into three main phases:

1. Formation of Schiff's base: The first phase involves the reaction between a reducing sugar (such as glucose or fructose) and the free amino group of a protein. This reaction forms a reversible Schiff's base or imine linkage (18). The reaction is as follows:

Reducing sugar + Amino group of protein → Schiff's base

2. Amadori rearrangement: The Schiff's base is relatively unstable and undergoes a rearrangement reaction known as Amadori rearrangement. During this step, the Schiff's base is converted into a more stable product called the Amadori product. This reaction typically occurs through the migration of a hydrogen atom and the formation of a new carbon-carbon double bond. The Amadori product is relatively stable compared to the Schiff's base, but it can still undergo further reactions leading to the formation of various AGEs (19).

Schiff's base → Amadori product

3. Formation of Advanced Glycation End Products (AGEs): In the final phase, the Amadori product can undergo further reactions, such as oxidation, dehydration, and cross-linking with other biomolecules. These complex reactions result in the formation of Advanced Glycation End Products (AGEs). The specific chemical structures of AGEs can vary widely, and they can be derived from proteins, lipids, or nucleic acids. Some common AGEs include Nε -(carboxymethyl) lysine (CML) and pentosidine (20).

Source of advanced glycation end products

Exogenous Source of AGEs

In the human body, the serum AGEs level can be elevated by both exogenous and endogenous sources. Exogenous sources of AGEs products include raw animal origin foods, fruits, and oils. Modern food processes like dry heat, irradiation, or ionisation significantly promote the formation of AGEs (21,22). Foods of animal origin and diets with a high proportion of fat and protein have high amounts of AGEs. Contrarily, AGEs levels were low in raw and even uncooked carbohydrate-rich diets like fruits, vegetables, milk, and whole grains (23-26) (Table 1). AGEs levels of more than 20,000 kU/day have been found in diets high in grilled or roasted meats, lipids, and highly processed meals (27-30). The wide spectrum of food products like milk and bakery products have pentosidine and pyrraline. Pyrraline is also found in the heated carrot sample, peanuts, puffed wheat, and soy sauce (23-26).

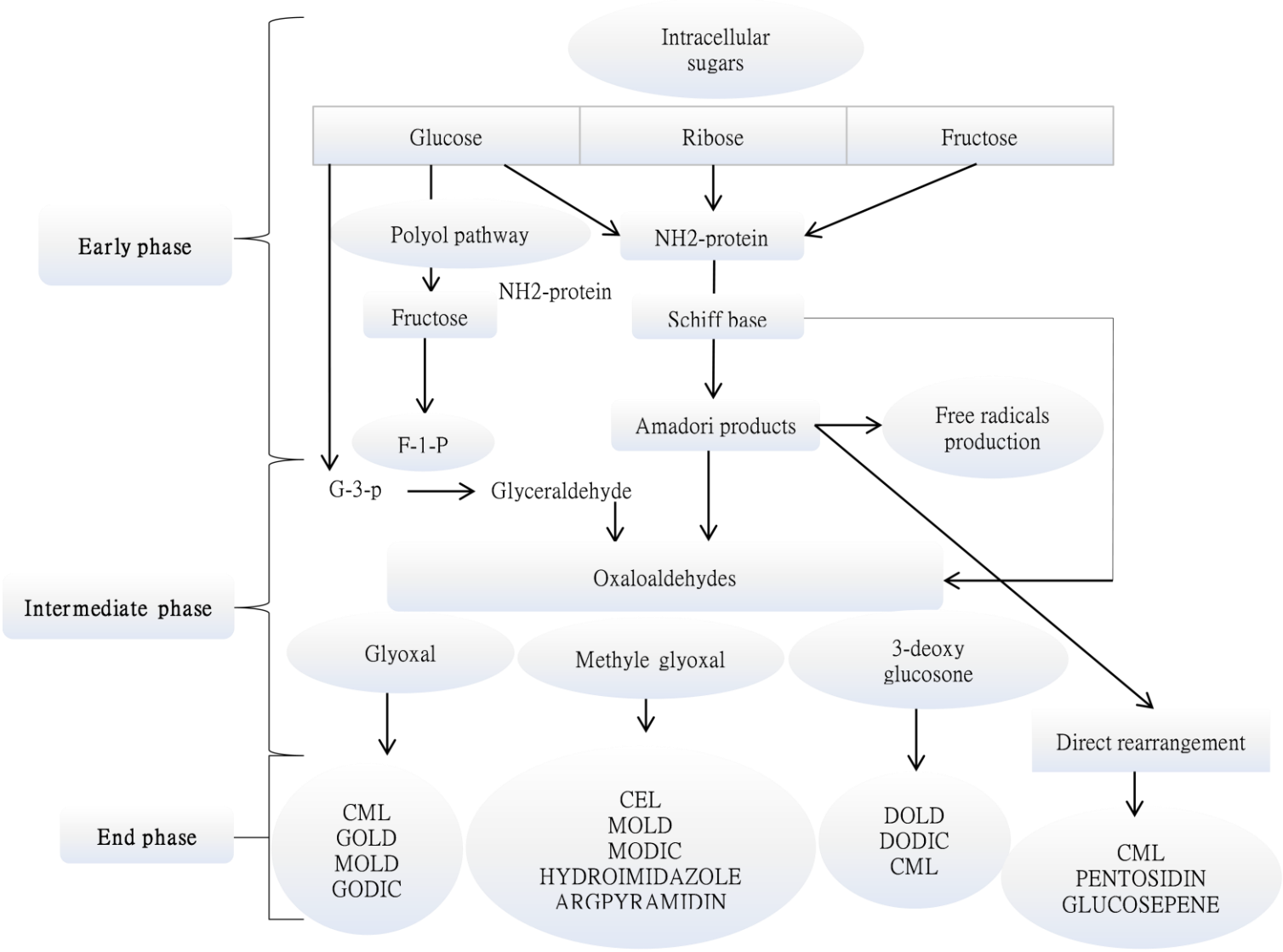

Figure 1. Factors Involved in Accelerating AGE Formation and Accumulation in the Body

Nonetheless, the growth pathway in actual food systems is more intricate and diversified due to the complexity of food matrixes and numerous reactions during food thermal processing; the precise formation mechanism of these in food products has not been extensively elucidated.

Endogenous Source of AGEs

Physiologically, AGEs are found in most human tissues and body fluids. HbA1c is the first endogenous glycation compound discovered, in which the valine residue at the N-terminus interacts with glucose to produce N-a-fructosylvaline (31).

When glucose, a-oxoaldehydes, and other saccharide derivatives interact non-enzymatically with proteins, nucleotides, and lipids, they produce AGEs products. (32). In addition, some intracellular sugars, such as fructose and glucose-6-phosphate, induce the synthesis of AGEs more quickly than glucose (33). The Schiff base/Amadori products and polyol pathways are the sources of endogenous AGE formation. Endogenous AGEs include the *in-vivo* AGE N-carboxymethyl lysine, as well as species like pyrraline, pentosidine, and N-carboxyethyl lysine (CEL) N-carboxy methyl lysine (CML) (34,35).

Table 1. N-Carboxymethyl-lysine (CML) content in various food products

Food Type	CML (mg/kg protein)	Method of estimation	Reference
Milk (Raw)	1.8	LCMS/MS	(25)
Milk (Pasteurized)	1.8	LCMS/MS	(25)
Milk (Skimmed)	4.7	LCMS/MS	(25)
Milk (Ultra-high temperature)	8.9	LCMS/MS	(25)
Milk (Infant formula regular)	76	LCMS/MS	(25)
Milk (Condensed)	205	LCMS/MS	(25)
Yogurt (low-fat)	89.3	UPLC-MS/MS	(26)
Whole Egg (Fried)	56.3	UPLC-MS/MS	(26)
Beef (Raw)	3.9	UPLC-MS/MS	(27)
Beef (Boiled)	27.3	UPLC-MS/MS	(27)
Beef (Fried)	61.1	UPLC-MS/MS	(27)
Chicken (Fried)	23.5	UPLC-MS/MS	(27)
Pork sausage (grilled)	210.1	UPLC-MS/MS	(26)
Bacon rasher (fried)	22.2	UPLC-MS/MS	(26)
Ham	11.5	UPLC-MS/MS	(26)
Salmon (poached)	52.9	ELISA	(28)
Salmon (grilled)	62.3	ELISA	(28)
Tuna (grilled)	86.9	ELISA	(28)
Kellogg's corn flakes	439.7	UPLC-MS/MS	(26)
Noodles (Boiled)	25.0	UPLC-MS/MS	(26)
Rice (Boiled)	4.8	LC-MS/MS	(29)
Rice (Fried)	8.1	LC-MS/MS	(29)
Muffin	126.3	UPLC-MS/MS	(26)
Chocolate	308.6	UPLC-MS/MS	(26)
Apple Pie	189.9	UPLC-MS/MS	(26)
Coffee	84.1	UPLC-MS/MS	(26)
Draft Beer	44.6	LC-MS/MS	(30)
Apple	39.3	UPLC-MS/MS	(26)
Banana	49.1	UPLC-MS/MS	(26)
Orange	76.7	UPLC-MS/MS	(26)
Tomato	10.2	UPLC-MS/MS	(26)
Potato Chips (fried)	19.6	LCMS-MS/MS	(29)
Tofu (fried)	49.9	LCMS-MS/MS	(29)
Soy Sauce	1.2	LCMS-MS/MS	(29)
Chew Sugar	195.8	UPLC-MS/MS	(27)
Chocolate	502.1	UPLC-MS/MS	(27)
Popcorn (Sweetened)	86.5	UPLC-MS/MS	(26)
Cereal chewy bar	436.8	UPLC-MS/MS	(26)
Ice Cream	128.1	UPLC-MS/MS	(26)
Butter	60.5	UPLC-MS/MS	(26)
Ketchup	12.9	UPLC-MS/MS	(26)
Mustard Dressing	13.7	UPLC-MS/MS	(26)

According to a recent study, the high dietary intake of simple sugar can be a significant source of endogenous AGEs. The riskiest endogenous source of sugar and a common sweetener for meals and beverages is fructose (36). Some in-vitro observational studies suggest that the reactivity of fructose is much higher than that of glucose as a glycation precursor (37).

Additionally, those who consume a lot of fructose-containing foods and beverages are more likely to develop insulin resistance, induce lipogenesis, have hypertriglyceridemia, and experience oxidative stress, which plays a significant role in the glycation process (38).

In the treatment of T2DM, empagliflozin (a sodium-glucose co-transporter-2 inhibitor) and liraglutide (a glucagon-like peptide 1 receptor agonist) are licensed by the FDA. However, these drugs can lead to hypotension and gallstones. Due to the limitations and side effects of current medicines, there is increased interest in studying natural compounds with different medical characteristics. These natural molecules show promise as potential novel medicines, delivering a safer and possibly more effective option. To improve

cardiovascular care, it is essential to comprehend their modes of action and possible synergies with existing therapies. The purpose of this review is to draw attention to the value of natural products in the management of CAD and the need for more studies in this field.

Natural products and their types

Natural products encompass a wide range of substances derived from plants, animals, and microorganisms. They are characterized by their origins in nature and have been used for centuries in traditional medicine and culinary practices (39). Natural products can be classified into several categories, including:

Phenolic Compounds: Phenolic compounds are a class of natural products characterized by their phenol rings. They are abundant in fruits, vegetables, nuts, and whole grains. Common phenolic compounds include flavonoids (e.g., quercetin, catechins), phenolic acids (e.g., chlorogenic acid, ferulic acid), and polyphenols (e.g., resveratrol). Many phenolic compounds exhibit potent anti-glycation properties due to their strong antioxidant and anti-inflammatory activities (40).

Terpenoids: Terpenoids are another diverse group of natural products found in plants, particularly in essential oils. Examples of terpenoids include limonene, carotenoids (e.g., lutein, beta-carotene), and terpenes (e.g., menthol). Some terpenoids have demonstrated the ability to inhibit glycation reactions and reduce the formation of AGEs (41).

Alkaloids: Alkaloids are nitrogen-containing compounds commonly found in plants, and they have various pharmacological activities. Examples include caffeine, nicotine, and quinine. While not as well-known for their anti-glycation effects as phenolic compounds (42).

Saponins: Saponins are glycosides found in various plant species, such as ginseng and soybeans. They have been studied for their anti-glycation properties, potentially through their ability to modulate glucose metabolism (43).

Anti-Glycation activity of natural products

The anti-glycation activity of natural products is primarily attributed to their antioxidant, anti-inflammatory, and carbonyl-trapping properties (44). Here are some mechanisms through which natural products combat glycation and inhibit AGE formation.

Antioxidant Activity: Many natural products, especially phenolic compounds, are potent antioxidants. They can scavenge free radicals and reactive oxygen species (ROS), reducing oxidative stress. By doing so, they prevent the oxidative modification of proteins and lipids, which is a key step in glycation and AGE formation (45).

Anti-Inflammatory Effects: Chronic inflammation is closely linked to glycation and AGE-related complications. Natural products with anti-inflammatory properties, such as curcumin from turmeric or omega-3 fatty acids from fish oil, can reduce inflammation and subsequently lower the risk of AGE formation (46).

Carbonyl Trapping: Some natural products contain functional groups (e.g., amino groups) that can trap and neutralize reactive carbonyl species, which are intermediates in glycation reactions. This carbonyl-trapping ability can inhibit the progression of glycation.

Modulation of Glycemic Control: Certain natural products, such as cinnamon and bitter melon, have been shown to improve glycemic control by enhancing insulin sensitivity and reducing blood glucose levels. By regulating blood sugar, they indirectly mitigate glycation reactions.

Natural AGEs inhibitors

When compared to synthetic drugs, natural products found to be generally safe for human ingestion. In recent years, researchers have looked at the ability of several plant extracts, fractions, and chemicals to suppress the production of AGEs (47,48). Because oxidative stress both accompanies and hastens the synthesis of AGEs, antioxidants appear to be a useful tool to avoid their creation. The

antiglycation potential of both plant-based materials and naturally occurring phenolic compounds with antioxidant properties has been investigated (49).

Some natural compounds can act as anti-AGES agents due to their antioxidant and quenching properties (Table 2) (50). Rutaceae family flavonoid compounds like those from the citrus genus have antioxidant properties and prevent the progression of chronic disease (51). Specifically, a component of citrus fruits (polymethoxyflavone) reduces inflammation and has an anti-proliferative effect on cancer (52). Methanolic extracts of two Scutellaria species, Scutellariaalpina and Scutellariaaltissima, as well as five

Table 2. List of plants resource their bioactive compounds with anti-AGEs property

S.NO.	Plants source	Bioactive compounds	Extract	Specific role	Study type	References
1	*Scutellariaalpina*	Flavonides (verbascoside ,baicalin, wogonoside and luteolin-7-glucoside)	Methanolic	Inhibit AGE formation	In vitro	(53)
2	*Scutellariaaltissima*	Flavonides(verbascoside, baicalin, wogonoside and luteolin-7-glucoside)	Methanolic	Inhibit AGE formation	In vitro	(53)
3.	*S. purpurea*	phenols, quercetin, chlorogenic acid, citric acid, tannins, anthraquinones, anthrone, coumarins, triterpenoids, and steroids (peel and seeds); quercetin, anthocyanins, proanthocyanidins, and flavonoids (peel); and saponins, leucoanthocyanidins, catechins, and flavanones	Ethanolic extract	Anti-Glycation activity	In vitro	(54)
4.	*Arachishypogaea*	quercetin, and chrysoeriol , luteolin, cinnamic acid, epicatechin, P-coumaric, isoquercitrin acid catechin, caffeic acid, rutin, trans-ferulic acid and resveratrol	80 % methanol extract	Anti-Glycation activity	In vitro	(55)
5	*Abiesbalsamea (L.) Mill.*	Gallocatechin derivatives	Ethanolic	Inhibit AGE formation	In vitro	(58)
6	*Alnusincana subsp. rugosa (Du Roi) R. T. Clausen*	Oregonins, rubranoside A & B, hirsutanone	Ethanolic	Inhibit AGE formation	In vitro	(58)
7	*Gaultheria hispidula (L.).*	Quercetin glycosides, glycoside, myricitrin, epicatechin, taxifolin, chlorogenic acid and catechin,	Ethanolic	Inhibit AGE formation	In vitro	(58)
8	*Juniperus communis L.*	2 kaempferol glycosides, Catechin, quercetin glycosides	Ethanolic	Inhibit AGE formation	In vitro	(58)
9	*Kalmia angustifolia L.*	myricetin, quercetin glycosides, Catechin, epicatechin	Ethanolic	Inhibit AGE formation	In vitro	(58)
10	*Larixlaricina Du Roi (K. Koch)*	piceatannolhydroxystilbenes , 2 diterpenes, Catechin, epicatechin resin acids	Ethanolic	Inhibit AGE formation	In vitro	(58)
11	*Lycopodium clavatum L.*	Ferulic acid derivatives, apigenin derivatives	Ethanolic	Inhibit AGE formation	In vitro	(58)
12	*Picea glauca (Moench.) Voss*	isorhamnetin glycosides, hydroxystilbenes ,Catechin, taxifolin, kaempferol, quercetinandlycopodine	Ethanolic	Inhibit AGE formation	In vitro	(58)
13	*Piceamariana (P. Mill) BSP*	Pungenin, hydroxy- and hydroxymethoxystilbenes	Ethanolic	Inhibit AGE formation	In vitro	(58)
14	*Pinus banksiana Lamb.*	(+)-Catechin, procyanidin B, taxifolin	Ethanolic	Inhibit AGE formation	In vitro	(58)
15	*Populus balsamifera L.*	Salicin, salicortin, salireposide, populoside, rubranoside	Ethanolic	Inhibit AGE formation	In vitro	(58)
16	*Rhododendron groenlandicum (Oeder) Kron& Judd*	procyanidins B1, B2, B3, quercetin glycosides, Chlorogenic acid, catechin,epicatechin, p-coumaric acid	Ethanolic	Inhibit AGE formation	In vitro	(58)
18	*Salix planifolia Pursh*	Salicin, isosalireposidederivatives, tremulacin	Ethanolic	Inhibit AGE formation	In vitro	(58)
19	*Sarracenia purpurea L.*	Cyaniding glycosides, Kaempferol, quercetin and goodyeroside, morronoside	Ethanolic	Inhibit AGE formation	In vitro	(58)
20	*Sorbus decora (Sarg.) C. K. Schneid.*	Catechin, epicatechin, uvaol,betulinic acid, 24-hydroxybetulin, 24-hydroxyuvaol, beta-amyrin, betulin,	Ethanolic	Inhibit AGE formation	In vitro	(58)
21	*Vaccinium vitis-idaea L.*	Benzoic acid, p-hydroxybenzoic acid, p-coumaric acid, p-coumaroyl-D-glucose, (+)-catechin, quercetin and cyaniding glycosides	Ethanolic	Inhibit AGE formation	In vitro	(58)

polyphenols from these plants, inhibited AGE synthesis significantly (53). Exposure to *S. purpurea* (ethenolic extract of leaves) to PC12 cells for glucose toxicity, which decreases glucose-mediated cell death significantly in a concentration-dependent manner (54). 80% methanolic extracts of *Arachishypogaea* (peanuts) contain higher levels of phenolics, which degrade AGEs already existing and stop the production of new AGEs (55). Additionally, pretreatment with peanut extracts significantly reduced the production of reactive oxygen species and cell death brought on by MGO in human umbilical vein endothelial cells (56). Saponins from Aralia taibaiensis (Araliaceae) protected against D-galactose-induced ageing in a rat model, implying that this saponin supplementation affects the AKT/Forkhead box O3a and Nrf2 pathways and increases antioxidant expression (57).

Other than plant extract, some plant metabolites (vitamins) and their derivatives show anti-AGE activity. Clinically, vitamins and their analogues are widely used as antioxidants. Vitamin C is a water-soluble vitamin with antioxidant properties (59). Infusion of vitamin C improves endothelial function and cardiac diastolic function (60). In diabetic patients, vitamin E can reduce lipid peroxidation, which can be used as a treatment of diabetic associated cardiovascular disease (61). Patients with haptoglobin genotype-2 (Hp2-2) who received vitamin E had a 35% lower risk of CVD in both type I and type II diabetes (62). Based on structure derivative form, vitamins B1 (Benfotiamine) and B6 (Pyridoxamine) may be effective metal chelators and effectively break collagen cross-linkers, which prevents the transformation of protein-Amadori intermediates to protein-AGE products, post-Amadori inhibitor by trapping carbonyl intermediates (63).

Conclusion

AGEs are the non-enzymatic reaction products of reducing sugars and proteins, lipids, or nucleic acids. Most AGEs are exogenous and endogenous: exogenous AGEs are food-derived (normal metabolism products). Deep-frying, grilling, and roasting are current trends in food preparation that raise the level of AGEs in food. However, endogenous AGEs produce different physiological forms in the human body, which vary depending on eating habits and bodily conditions like diabetes. These AGEs cause arterial stiffness and systolic and diastolic dysfunction by affecting extracellular matrix proteins (collagen and laminin). Further, these AGEs bind with RAGE, activate many signalling pathways, and generate oxidative stress and inflammation, causing vascular dysfunction. Overall, AGEs are major contributing factors in the pathophysiology of cardiovascular disease.

Because the synthesis of AGEs in vivo has been linked to the aetiology of numerous chronic diseases, particularly diabetic complications, including CAD, So, AGEs reduction has been demonstrated to be a successful strategy. In general, AGEs inhibitors work to reduce oxidative stress and glycoxidation by trapping or scavenging certain intermediates, including reactive dicarbonyls, free radicals, and nitrogen species generated during glycation, as well as by dissolving established AGE crosslinks. Aspirin and diclofenac inhibit early stages of AGEs synthesis, intermediate stages are inhibited by pioglitazone, metformin, and phenacylthiazolium bromide, and AGEs crosslinking and intermediate stages are inhibited by aminoguanidine. Furthermore, methanolic extracts of Scutellariaalpina, Scutellariaaltissima, Albiziaodoratissima, and ethenolic extract of Scutellariapurpurea significantly lower blood AGE levels and their capacity to induce disease by targeting several molecular pathways. A variety of plant metabolites, including pyridoxine, benfotiamine, piceatannol, rosmarinic acid, lithospermic acid, quercetin, and kaempferol, also inhibit AGE synthesis at different stages. Pyridoxine is presently being investigated in RCTs. Current RCTs must prove end-organ

protection in chronic illnesses like diabetes. Additionally, these natural anti-glycation agents have a sufficient ability to reduce oxidative stress and inflammation and can significantly decrease the risk of cardiovascular disease.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Authors' contributions

PK.D. conceived & designed the study. D.S. extracted literature and prepared the draft. PK.D and D.S. contributed data analysis. MM.AB. and Q.M did critical review of paper. PK.D. did the final review. All authors read and approved the final manuscript.

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